REMARKS

Claims 1, 4, 7, 8, 10-13, and 15-19 are pending.

Applicants herein submit a Request for Continued Examination (RCE).

Applicants acknowledge the Examiner's maintained rejection of claims 1, 4, 7-8, 10-13, and 15-19, under 35 U.S.C. § 112 ¶1, based on alleged lack of *written description* for contiguous CpG island sequence that comprise SEQ ID NO:36 or 37. Applicants have amended the claims to obviate this rejection.

Applicants acknowledge the Examiner's maintained rejection of claims 1, 4, 7-8, 10-13, and 15-19 under 35 U.S.C. § 112 ¶1, based on alleged lack of *enablement*. Applicants have amended the claims to obviate this rejection.

No new matter has been added.

Rejections under 35 U.S.C. § 112, ¶1

Written description:

The Examiner has maintained the rejection of claims 1, 4, 7-8, 10-13, and 15-19, under 35 U.S.C. § 112 ¶1, based on alleged lack of written description for "contiguous CpG islands that comprise of SEQ ID NO:36 and 37.

Specifically the Examiner urges (citing The Regents of the University of Calif. v. Eli Lilly) that a generic statement defining a genus of nucleic acids by function is not enough to provide adequate written description (Office Action of 08 November 2005 at page 4).

Applicants respectively reassert and reaffirm the arguments of record, that in the present case applicants do not merely define a genus by functional activity, but rather the specification at page 5 and 8 teaches a formula; namely, "a CpG island sequence associated with a particular SEQ ID NO sequence of the present invention is that contiguous sequence of **genomic** DNA that encompasses at least one nucleotide of the particular SEQ ID NO sequence, and satisfies the criteria of having both a frequency of CpG dinucleotides corresponding to an Observed/Expected Ratio >0.6), and a GC Content >0.5." Physical properties and structure are also implicit within this definition, because the sequence is anchored at a precise genomic position, and the definition

absolutely requires that the associated sequence is contiguous with the portion of the CpG island. Contrary to the Examiner's urging, the recited genera (CpG island sequences comprising SEQ ID NO:36 [or 37]) are not merely defined by functional language, but rather are explicitly defined by the core SEQ ID NO:36 sequence and the recited formula describing the larger CpG island, and the fact that the sequence is anchored at a precise genomic position. Therefore, the larger genomic CpG island is adequately defined and described by the core sequence and the formula.

Applicants point out that the Examiner's own example (see Office Action page 4):

**********(SEQ ID NO:36)*******(CpG)******

Illustrates that applicants' written description is adequate and commensurate in scope with the instant claims, because it has enabled the Examiner to present a species of applicants' claimed genus, based on the specification teachings; the core SEQ ID NO:36 and applicants CpG island formula and the fact that this is a contiguous genomic sequence. Additionally, as taught by applicants, and as recognized by the Examiner in presenting this example, the CpG dinucleotide sequences are the precise defined sequences that are assayed, regardless of their position within the larger CpG island, in determining methylation state. A representative number of sequences is provided by the fact that SEQ ID NO:36 is explicitly recited in the context of a contiguous 0.2 to about 1Kb according to the disclosed formula and definition of CpG island. For example, the following are species in the size range of 0.2 to 1.Kb are represented in the specification:

**********(SEQ ID NO:36)*******(CpG)******
**********(SEQ ID NO:36)*******(CpG)****
**********(SEQ ID NO:36)*******(CpG)**
**********(SEQ ID NO:36)*******(CpG)******
*******(SEQ ID NO:36)*******(CpG)****
(SEQ ID NO:36)****(CpG)**
*(SEQ ID NO:36)*******(CpG)*

Applicants, for reasons already of record in this case, fundamentally disagree with the Examiner's conclusions with respect to the written description analysis but have nonetheless amended claims 1 and 13 to delete the recitation of contiguous CpG island sequences.

Applicants, therefore, respectfully request withdrawal of the Examiner's rejection of claims 1, 4, 7-8, 10-13 and 15-19 under 35 U.S.C. § 112 ¶1, based on alleged lack of written description.

Further Rejections under 35 U.S.C. § 112, ¶1

Enablement:

The Examiner has maintained rejections of claims 1, 4, 7-8, 10-13, and 15-19 under 35 U.S.C. § 112 ¶1, based on alleged lack of enablement in view of recitation of contiguous CpG islands.

Applicants, for reasons already of record in this case, fundamentally disagree with the Examiner's conclusions with respect to the enablement analysis but have, as discussed herein above, amended claims 1 and 13 to delete the recitation of contiguous CpG island sequences.

Applicants reaffirm and reassert the Declaration of Dr. Cathy Lofton Day, already of record, and which will therefore not be reiterated herein.

We are in agreement with the Examiner that Toyota teaches "examples where CpG islands act independently." However, that is not the relevant question here. The relevant question is whether the CpG dinucleotide sequences within a given CpG island behave coordinately. Here, the teachings of Toyota are in agreement with the applicants currently recited claims.

Specifically, Toyota initially describes/defines a large 4Kb region, based on a definition of having a GC content of 0.67; CpG/GpC ration of 0.78; and a total of 305 CpG sites in a 4-kb region (Toyota at pate 4536 column 2 middle of 1st full para), and divides this 4kb region into 8 subregions. However, Toyota notes that this region is considerably larger that typical CpG islands (Toyota at page 4537, column 2, 1st full para), and he explicitly concludes that "with regards to hypermethylation in cancer, the CpG-rich region upstream of CACNA1G appears to be composed of two CpG islands that behave independently" (MINT31 regions 1 and 2 corresponding to the

upstream CpG island 1; the 5' regions 5-7 of CACNA1G in the downstream CpG island 2; and regions 3, 4 and 5 between CpG island 1 and 2, behaving differently. Toyota concludes (page 4540, at end of carryover para) that "methylation of MINT 31 appears to be independent of methylation of CACNA1G, suggesting that they are two distinct CpG island regulated by different mechanisms." Significantly, therefore, Toyota teaches that while different CpG islands within a gene area can behave differently or independently, the subregions within a given CpG island, for example regions 1 and 2 of island 1 and regions 5-7 of island 2, behave coordinately and define the behavior of the CpG island which comprises the subregions.

Therefore, Toyota like the vast bulk of art in this area, is fully consistent with the teachings of the present invention which teach that the CpG dinucleotides within a given contiguous CpG island are coordinately methylated.

The teachings of Pao that not all CpGs in a CpG island were hypermethylated even when adjacent to CpGs that were hypermethylated (*e.g*, that some adjacent CpGs were resistant or protected from hypermethylation), does not run counter to applicants recitation of coordinately methylated CpGs, because applicants recitation does not require that *all* CpGs within a CpG island are coordinately methylated, but rather only that the methylation change (*e.g*, hypermethylation) of the those CpGs that are differentially methylated between normal and cancer, is a methylation change that is coordinate, so that all differentially methylated CpG are either up-methylated (hypermethylated to some extent), or all down-methylation (hypomethylated to some extent). Applicants claims reflect the fact that within a particular CpG island, the change in methylation of those CpGs that do undergo a methylation change, is coordinate (i.e., coordinately hypermethylated or coordinately hypomethylated). It is irrelevant that some CpGs are protected from, or resist hypermethylation for example. The claims are drawn to coordinately methylated CpGs with the CpG island, and do not necessarily require that *all* CpGs are differentially

methylated between normal and cancer. In fact the CpGs of Pao follow this pattern in that while not all CpGs participate in differential methylation between normal and abnormal tissue, those that do participate do so in a generally coordinate way, although the extent of hypermethylation is not identical between differentially methylated CpGs there is nonetheless coordinate methylation.

The Examiner's urging that teachings of Cameron that the p15 CpG island methylation is heterogeneous, and thus not support that a single dinucleotide may be representative of an entire CpG island is unsupportable, because the methylation heterogeneity characterized in Cameron relates to heterogeneity in the specific CpGs sites hypermethylated between alleles. That is, like Pao, not all CpGs on both alleles undergo hypermethylation. However, those CpGs that do show hypermethylation are coordinately hypermethylated.

Therefore, Applicants respectfully contend that the Examiner's position is entirely unsupportable in view of Toyota, Pao, and Cameron, and that these references actually support Applicants' position or coordinate hypermethylation within a CpG island.

Moreover, given the instant teachings and the state of the art, and fully consistent with Toyota cited by the Examiner, Applicants contend that it would not entail undue experimentation to determine whether a CpG dinucleotide of the contiguous CpG islands that respectively comprise SEQ ID NO:36 or 37 is coordinately methylated with a CpG of SEQ ID NO:36 or 37. This is precisely what would be expected as described above, and in view of Toyota, Pao, and Cameron cited by the Examiner. Such a CpG island is readily identifiable and analyzable because it is structurally defined as being contiguous to Applicants' disclosed SEQ ID NOS:36 or 37, and is further defined and describe by Applicants' formula describe herein above. The level of skill in the art is high, and given the instant teachings and those of the art, isolation of such a CpG island sequence from a cancer tissue and determining the methylation state of one or more CpG residues therein relative to a control, could be done by one of ordinary skill in the art in a matter of a few

days or a week using standard DNA manipulation methods and methylation assays available at the time of filing of the present application.

The Declaration by Dr. Kurt Berlin (already of record) is in support of the present Response and Amendment. The Declaration describes a paper (Eckhardt et al., *Nat Genet*. 2006 Dec;38(12):1378-85. Epub 2006 Oct 29) further confirming, as was appreciated in the art at the time of filing and as taught in the instant specification, that there is a significant correlation for co-methylation within CpG dense regions (*e.g.*, CpG islands) over the distance of up to at least 1,000 nucleotides in each direction from a particular determined CpG (see, *e.g.*, page 2, column 2, 1st full paragraph, of attached publication document). The Declaration additionally comments on and rebuts the Examiner's contentions, based on Toyota et al.

The fact that the Echkardt paper cited in the Berlin Declaration was available 6 years after filing, and stated that "our data suggest DNA methylation to be ontogenetically more stable than previously thought" does not indicate, as urged by the Examiner that there was no appreciation for coordinate methylation at the time of filing, as the present record supports.

In light of the scope of the claims, the teachings in the specification, the presence of specific working examples in the specification, the high level of skill of those in this art, the knowledge of those of skill in this art, and the predictability of the subject matter, it would not require undue experimentation for a person of skill in the art to practice the invention as claimed. Therefore, the specification is enabling for making and using the full scope of the claimed subject matter.

Applicants respectfully request that the rejection be reconsidered and withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request entry of

the present Response and Amendment, and allowance of all pending claims. The Examiner is encouraged to phone Applicants' attorney, Barry L. Davison, to resolve any outstanding issues and expedite allowance of this application.

Davis Wright Tremaine LLP
1201 Third Avenue, Suite 2200
Seattle, Washington 98101-3045
Telephone: 206-757-8023
Facsimile: 206-757-7023

Respectfully submitted,
Markl et al.,
Davis Wright Tremaine LLP

/Barry L. Davison, Ph.D., J.D./
Barry L. Davison, Ph.D., J.D.
Attorney for Applicant
Registration No. 47,309